Remarks

The present invention is directed to compositions and methods for immunization against an allergen. Claims 16 and 25 have been amended to address the Examiner's claim objections. Support for these amendment is found in the original claims. These amendments do not add new matter. Claims 1-15, 21, 22 and 28-32 are cancelled. Claims 16-20 and 23-27 are pending in the instant application.

Claim Objections

Claims 16 and 25 are objected to because Claims 16 and 25 are dependent upon non-elected base claims 1-13. Claims 16 and 25 have been amended to no longer depend on claims 1-13. Withdrawal of this objection is respectfully requested.

Rejections under 35 U.S.C. § 112, first paragraph (enablement)

Claims 16-20 and 23-27 are rejected under 35 U.S.C. 112, first paragraph, for failing to satisfy the enablement requirement. Applicants respectfully traverse this rejection as it applies to the amended claims.

The Examiner has rejected Claims 16-20 and 23-27 under U.S.C. 112, first paragraph, for lacking enablement because she believes that the specification only discloses, and is therefore only enabling for: a method for immunization against an allergen comprising administering the recombinant nucleic acid of SEQ ID NO:5 by intramuscular administration and the native Der p 1 allergen to the subject intraperitoneally and subsequently by aerosol in combination with an adjuvant, wherein the nucleic acid is administered in the first phase over a period of time sufficient to induce long term immune memory in the subject, and wherein multiple doses of the

nucleic acid is administered in the first phase over a period of about a year. The Examiner asserts that the specification is not reasonably enabling for:

(a) all whole allergens, other than the Der p 1 sequence of SEQ ID NO: 5 and the native Der p 1 protein;

(b) all T helper cell epitopes, antigenic fragments containing one or more T helper cell epitopes and functional equivalents of the allergens in (a);

(c) all recombinant nucleic acids encoding the genus of all the aforementioned whole allergens, and T helper cell epitopes, antigenic fragments containing one or more T helper cell epitopes and functional equivalents thereof;

(d) the genus of all "signal" and "targeting" peptides;

(e) the genus of all N-terminal signal peptides of LAMP-I, human tissue plasminogen activator, LAMP-II, DEC-205, P-selectin, tyrosinase, GLUT4, endotubin and Nef;

(f) the genus of all C-terminal lysosome or endosome targeting sequences of LAMP-I, human tissue plasminogen activator, LAMP-II, DEC-205, P-selectin, tyrosinase, GLUT4, endotubin and Nef;

(g) the genus of all transmembrane and cytoplasmic domains of LAMP-I or functional equivalents thereof; and

(h) the claimed method of "preventing" (100% prevention) the occurrence of allergy by administration of the claimed compositions.

The Examiner asserts that the specification is non-enabling for the above items (a) – (h) because the specification lacks sufficient direction / guidance and working examples to enable a person skilled in the art to practice the invention without an undue amount of experimentation.

Applicants respectfully disagree with the Examiner for the reasons set out below.

With regards to item (a), the Examiner asserts that allergens other than the Der p 1 sequence of SEQ ID NO: 5 and the native Der p 1 protein are not enabled because the specification fails to provide guidance regarding which allergen sequences other than the Der p 1 sequence of SEQ ID NO: 5 and the native Der p 1 protein would work in the claimed invention. Applicants must disagree with the Examiner's assertion because paragraph [0041] of the specification provides a list of all the allergens that would work in the claimed invention; these include Blo t 1, Blo t 5, Der p 1, Der p 2, Der p 3, Der f 1, Der f 2 and Der f 3. Furthermore, Examples 3 and 4 as well as Figs. 1 to 8 are all directed to the allergen Blo t 5. The Blo t 5 gene is comprised within the recombinant nucleic acids SEQ ID NOs: 2, 3 and 4 (see also paragraphs [0096], [0097] and [0098]). Hence, contrary to the Examiner's assertion, Applicants submit that the specification clearly provides sufficient guidance and working examples on allergen sequences other than the Der p 1 sequence of SEQ ID NO: 5 and the native Der p 1 protein that would work in the claimed invention. Accordingly, Applicants submit that the specification is enabling for whole allergens other than the Der p 1 sequence of SEQ ID NO: 5 and the native Der p 1 protein, and that the scope of the claims should not be limited only to the Der p 1 sequence of SEQ ID NO: 5 and the native Der p 1 protein.

The Examiner also asserts that the structures of all the allergens are not known, and hence the present claims would encompass presently as yet unidentified allergens. Applicants submit that the cloning and sequencing of genes in general are routine and known to those skilled in the art. Furthermore, paragraph [0041] of the specification lists several exemplary publications that would provide sufficient guidance to those skilled in the art to clone and sequence allergen genes for use in the recombinant nucleic acids of the claimed invention.

With regards to item (b), Applicant submits that exemplary T helper cell epitopes, antigenic fragments containing one or more T helper cell epitopes and functional equivalents of the allergens in item (a) that would work in the present invention are taught in paragraph [0037], in Example 3, and in Figs. 3 to 7 of the specification. Paragraph [0037] teaches that useful fragments and T helper cell epitopes may be identified using computer-assisted analysis of amino acid sequences as known in the art. Example 3 describes the experimental protocol and data shown in Figs. 3 to 7. Fig. 3 shows the induction of specific Th1 humoral and cellular immune responses in mice injected with a DNA vaccine encoding a chimeric protein comprising the Blo t 5 gene fragment that encodes the 1-2^d-restricted Th epitope, while Figs. 4 to 7 show the induction of immune responses in mice injected with a DNA vaccine encoding a chimeric protein comprising the Blo t 5 gene fragment that encodes H-2^d-restricted Th epitope (see also SEQ ID NO: 2 at paragraph [0096]).

With regards to the "functional equivalents," Applicants submit that paragraphs [0038] to [0040] provide guidance on the functional equivalents that would work with the present invention, and how to obtain / identify such functional equivalents. For example, exemplary conservative amino acid substitutions that could be used without adversely affecting the function of the allergens are listed in paragraph [0038], while sufficient guidance to those skilled in the art on how to identify functional equivalents of allergens are provided in paragraphs [0039] and [0040]. Briefly, allergens from different species can be compared and the conserved sequences identified. The more divergent sequences are more likely to tolerate sequence changes. The sequences may also be modified using computer-assisted analysis of probable T- and/or B-cell epitopes. The functional equivalents may be identified by immunizing an animal, for example a

mouse, with the putative equivalent, challenging the animal with the allergen and determining whether the equivalent confers protective immune response against the allergen.

Hence, contrary to the Examiner's assertion, Applicants submit that the specification clearly provides sufficient guidance and working examples on T helper cell epitopes, antigenic fragments containing one or more T helper cell epitopes and functional equivalents of the allergens in item (a) that would work in the present invention.

With regards to item (c), the Examiner asserts that the specification is not enabled for all recombinant nucleic acids encoding the genus of all the aforementioned allergens. Applicants submit that paragraph [0041] teaches house dust mite species, the genes of which would work in the present invention. These are *Blomia tropicalis, Dermatophagoides pteronyssinus,* and *Dermatophagoides farinae*. Furthermore, as noted above, paragraph [0041] of the specification lists several exemplary publications that would provide sufficient guidance to those skilled in the art to clone and sequence allergen genes, regardless of genus/species, for use in the recombinant nucleic acids of the claimed invention.

With regards to items (d) to (g), the Examiner asserts that the specification does not disclose the genus of all "signal" and "target" peptides, N-terminal signal peptides of LAMP-I, human tissue plasminogen activator, LAMP-II, DEC-205, P-selectin, tyrosinase, GLUT4, endotubin and Nef, C-terminal lysosome or endosome targeting sequences of LAMP-I, human tissue plasminogen activator, LAMP-II, DEC-205, P-selectin, tyrosinase, GLUT4, endotubin and Nef, and transmembrane and cytoplasmic domains of LAMP-I or functional equivalents thereof.

Applicants must disagree with the Examiner on item (d) because the specification does provide exemplary "signal" and "target" peptides from *Rattus norvegicus* (see for example SEQ ID NOs: 7, 8, 23, 24, 27, 28, 43, 44), *Mus musculus* (see for example SEQ ID NOs: 2-5, 11-12,

15, 16, 25, 26, 31, 32, 35, 36, 45, 46), and *Homo sapiens* (see for example SEQ ID NOs: 6, 9, 10, 13, 14, 17-22, 29, 30, 33, 34, 37-42, 47, 48). Figs. 3-10 and Examples 3 to 5 teach the use of the LAMP-I signal peptide from *Mus musculus*, while Figs. 11-12 and Example 6 teach use of the *Homo sapiens* tissue plasminogen activator signal peptide from *Homo sapiens* (SEQ ID NO: 6).

Applicants also disagree with the Examiner on item (e) because N-terminal signal peptides that would work in the present invention are listed in paragraph [0032]. These include *Homo sapiens* tissue plasminogen activator (SEQ ID NO: 48) as used in the chimeric gene SEQ ID NO: 6 (Example 6, Figs. 11 and 12); lysosomal membrane protein LIMP-II (SEQ ID NOs: 7, 9, 11, 27, 29, 31); DEC-205 (SEQ ID NOs: 13, 15, 33 and 35); P-selectin (SEQ ID NOs: 17 and 37); tyrosinase (SEQ ID NO: 19 and 39); GLUT4 (SEQ ID NOs: 21 and 41); endotubin (SEQ ID NOs: 23 and 43); and Nef.

Applicants further disagree with the Examiner on item (f) because C-terminal lysosome or endosome targeting sequences that would work in the present invention are listed in paragraph [0036]. These include LAMP-I (SEQ ID NOs: 26, 46); human tissue plasminogen activator; LIMP-II (SEQ ID NOs: 8, 10, 12, 28, 30 and 32); DEC-205 (SEQ ID NOs: 14, 16, 34 and 36); P-selectin (SEQ ID NOs: 18 and 38); tyrosinase (SEQ ID NOs: 20 and 40); GLUT4 (SEQ ID NOs: 22 and 42); endotubin (SEQ ID NOs: 24 and 44); and Nef.

With regards to item (g) on the transmembrane and cytoplasmic domains of LAMP-I or functional equivalents thereof, Applicants re-iterates that guidance on the functional equivalents of the transmembrane and cytoplasmic domains of LAMP-I that would work in the present invention, and methods for obtaining / identifying such functional equivalents are set out in paragraphs [0038] to [0040].

With regards to item (h), the Examiner asserts that the present specification fails to provide guidance on how to totally prevent (100% prevention) allergy using the claimed compositions. Claim 25 is amended to read as "[a] method for treating or prophylaxis of an allergic reaction...." A prophylactic result can be the inhibition of the rate of a reaction or allergic disease onset or progression (see paragraph [0072]) and not necessarily a 100% prevention is required. Furthermore, prophylactically effective amounts are taught in for example paragraph [0073]; these are from about 100 μg to 5000 μg, preferably 200 μg to 2000 μg.

In view of the above, Applicants submit that the Examiner is incorrect to assert that the specification is only enabling for a method for immunization against an allergen comprising administering the recombinant nucleic acid of SEQ ID NO: 5 by intramuscular administration and the native Der p 1 allergen to the subject intraperitoneally and subsequently by aerosol in combination with an adjuvant, wherein the nucleic acid is administered in the first phase over a period of time sufficient to induce long term immune memory in the subject, and wherein multiple doses of the nucleic acid is administered in the first phase over a period of about a year. Recombinant nucleic acids other than SEQ ID NO: 5 (such as SEQ ID NOs: 2, 3, 4 and 6, comprising various combinations of exemplary signal peptides, allergens, and target peptides as discussed above) are clearly taught in the present specification. Administration of these recombinant nucleic acids via other routes (i.e. other than the intramuscular route) such as the intradermal route (see paragraphs [0090], [0115]) and oral route (see paragraphs [0092], [0127]) are also clearly taught in Examples 3 and 6. Allergens other than Der p 1, such as Blo t 1, Blo t 5, Der p 2, Der p 3, Der f 1, Der f 2 and Der f 3 are also taught as set out above – see in particular Figs. 3 to 8 and Example 3 where the Blo t 5 protein is used.

Accordingly, Applicants submit that pending claims 16-20 and 23-27 meet the enabling requirement because, for the reasons set out above, the present specification provides sufficient direction / guidance and working examples to enable a person skilled in the art to practice the invention without an undue amount of experimentation. The protocols and data in Examples 1-6 (using various permutations of the signal peptides, allergens, and targeting peptides) clearly demonstrate the enablement of the various embodiments of the claimed invention.

Rejections under 35 U.S.C. § 112, first paragraph (written description)

Claims 16-20 and 23-27 are rejected under 35 U.S.C. 112, first paragraph, for failing to satisfy the written description requirement. Applicant respectfully traverse the rejection as it applies to the amended claims.

The Examiner has rejected Claims 16-20 and 23-27 under U.S.C. 112, first paragraph, for not satisfying the written description requirement because the Examiner asserts that, other than the specific recombinant nucleic acid of SEQ ID NO: 5 and Der p 1 allergen, there is inadequate written description of the structure and functions for any other recombinant nucleic acids and allergens as set forth in the claims.

Applicants must again respectfully disagree with the Examiner for the reasons already set out above in Section (B) above regarding the enablement rejection. Applicants respectfully assert that the Examiner is construing the written description requirement too stringently.

Applicants re-iterate that other recombinant nucleic acids (SEQ ID NOs: 2-4, 6) are clearly taught and described in the present specification. SEQ ID NO: 2 is directed to a recombinant nucleic acid that comprises the *Mus musculus* LAMP-I leader sequence, the Blo t 5 gene fragment for the H-2^d-restricted Th epitope and the *Mus musculus* LAMP-1 transmembrane

and cytoplasmic domain. SEQ ID NO: 3 is directed to recombinant nucleic acid that comprises the *Mus musculus* LAMP-I leader sequence, the entire Blo t 5 gene and the *Mus musculus* LAMP-1 transmembrane and cytoplasmic domain. SEQ ID NO: 4 is directed to a recombinant nucleic acid that comprises the *Mus musculus* LAMP-I leader sequence and the entire Blo t 5 gene. SEQ ID NO: 6 is directed to a recombinant nucleic acid that comprises the *Homo sapiens* tissue plasminogen activator leader sequence, the entire Der p 1 gene and the *Mus musculus* LAMP-1 transmembrane and cytoplasmic domain. See also paragraphs [0044] and paragraphs [0045] – [0046] describing promoters that could be used in these recombinant nucleic acids and methods of construction of these recombinant nucleic acids, as well as paragraphs [0096] – [0098] and [0100] that describe the structural make-up of these recombinant nucleic acids. The functions and activity of these recombinant sequences are demonstrated in Figs. 3-8 and 11-12 and Examples 3, 4 and 6.

Applicants also re-iterates the above submission that other allergens (i.e. other than Der p 1) such as Blo t 1, Blo t 5, Der p 2, Der p 3, Der f 1, Der f 2 and Der f 3 are clearly taught and described in the present specification. In particular, the Blo t 5 allergen (SEQ ID NO: 50) has been used in the various recombinant nucleic acid constructs as set out above, in Examples 3 and 4 and in Figs. 1-8.

Conclusions

Applicants submit that the response herein provides a complete response to the Office Action dated November 28, 2008.

If the Examiner believes there are other issues that may be resolved by telephone interview, or that there are any informalities remaining in the application that may be corrected by Examiner's Amendment, a telephone call to the undersigned is respectfully solicited.

No additional fees are believed due, however the Commissioner is hereby authorized to charge any additional fees that may be required, or credit any overpayment of fees to Deposit Account number 11-0980.

Respectfully submitted,

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